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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/980,762	09/03/2002	David B Weiner	UPAP-0495	8614

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EXAMINER	
OUSPENSKI, ILIA I	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 04/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/980,762	WEINER ET AL.	
	Examiner	Art Unit	
	ILIA OUSPENSKI	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 October 2005 and 17 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,10-13,16-22 and 41-81* is/are pending in the application.

4a) Of the above claim(s) *16-22,48-54,61-67 and 75-81* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,10-13,41-47,55-60 and 68-74* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/20/02,12/4/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendments/remarks, filed 10/03/2005 and 01/17/2006, are acknowledged.

Claims 3 – 9, 14 – 15, and 23 – 40 have been cancelled.
Claims 41 – 81 have been added.
Claims 1 – 2, 10, 12, 13, 16, 55, and 57 have been amended.

Claims 1 – 2, 10 – 13, 16 – 22, and 41 – 81 are pending.

2. Applicant's election with traverse of Group III (drawn to a nucleic acid encoding a chimeric protein which does not include the C domain of CD80, and vectors and compositions thereof, corresponding to original claims 9 – 15, and to presently amended claims 1 – 6, 10 – 13, 41 – 47, 55 – 60, and 68 – 74) in the reply filed on 01/17/2006 is acknowledged.

The traversal is on the grounds that addition of Group VI in the examination allegedly would not present and undue burden to the Office.

This is not found persuasive because burden on the Office in not considered as grounds for finding lack of unity of invention applications filed under 35 USC 371. See MPEP 1893.03(d). The Groups have been found lack unity of invention, because they do not relate to a single general inventive concept under PCT Rule 13.1, as discussed in detail in the previous Office Action.

The requirement is still deemed proper and is therefore made FINAL.

Applicant further elects the Species wherein the chimeric protein comprises the set of domains set forth in claim 69.

3. Claims 16 – 22, 48 – 54, 61 – 67, and 75 – 81 are withdrawn from further consideration by the Examiner, under 37 C.F.R. § 1.142(b), as being drawn to nonelected inventions.

Claims 1 – 2, 10 – 13, 41 – 47, 55 – 60, and 68 – 74 are under consideration in the instant application.

4. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth herein.

Upon review of the instant application, it is noted that the sequences disclosed at least in Table 6 *are not accompanied by SEQ ID Numbers*. Applicant is reminded of the sequence rules which require a submission for all sequences of more than 9 nucleotides or 3 amino acids (see 37 CFR 1.821-1.825) and is also requested to carefully review the submitted specification for any and all sequences which require compliance with the rules. Applicant is reminded to amend the specification and the claims accordingly.

Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825) in response to this Office Action.

5. Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. The provisional application USSN 60/131,764 upon which priority is claimed appears to provide adequate support under 35 U.S.C. 112 for subject matter claimed in the instant application.

6. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because: Non-initialed and/or non-dated alterations have been made to the oath or declaration, relating to the mailing address and citizenship of co-inventor Michael Agadjanyan. See 37 CFR 1.52(c).

7. Applicant's IDS documents, filed 11/20/2002 and 12/04/2003, are acknowledged, and have been considered.

It is noted that where only an abstract of the reference has been provided, only the abstract has been considered. It is also noted that certain references have been considered, but lined through as they are not appropriate for printing on the face of a Patent.

8. The use of trademarks has been noted in this application (e.g. Triton X-100 on page 46). Each letter of the trademarks should be capitalized wherever it appears and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

9. Claim 1 is objected to because of the following informalities: in the phrase "wherein said coding sequence that encodes a CD80 mutant protein that comprises []," the first recitation of "that" appears to be superfluous. Appropriate correction or clarification is required.

Claim 43 is objected to because of an apparent typographical error in the phrase "nucleic molecule," where apparently "nucleic acid molecule" was intended. Appropriate correction is required.

10. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 1 – 2, 10 – 13, 41 – 47, 55 – 60, and 68 – 74 are rejected under **35 U.S.C. 112, second paragraph**, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 1 – 2, 10 – 13, 41 – 47, 55 – 60, and 68 – 74 are indefinite in the recitations of "functional 80C" and "functional fragment," because it is unclear which functions are encompassed by the claim. One of ordinary skill in the art would be aware that costimulatory molecules like CD80 possess multiple functions, including, for example, affecting T cell survival, cell cycle progression, migration, and cytokine secretion. Therefore, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the claimed invention.

B. Claims 1 – 2, 10 – 13, 41 – 47, 55 – 60, and 68 – 74 are indefinite in the recitation of "80C," because, unlike other domains of the claimed molecule (e.g. 80V, or 86C), "80C" is not defined by the claim, and in the absence of a definition, the metes and bounds of the claimed subject matter are unclear.

C. Claims 1 – 2, 10 – 13, 41 – 47, 55 – 60, and 68 – 74 are indefinite in the recitation of "said CD80" in the last part of claim 1, because it is unclear whether the recitation refers to wild-type or mutant CD80.

D. Claims 1 – 2, 10 – 13, 41 – 47, 55 – 60, and 68 – 74 are indefinite in the recitation of "transmute the negative signal" in claims 1 and 55, because the meaning of the word "transmute" appears to be inconsistent with the context of the respective claims. It appears that "transmit" was intended. It is noted, however, that the specification at least at pages 4 and 5 contains the phrase "transmute the negative signal," therefore, it is unclear whether this is a typographical error or a vague and indefinite phrase. One of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the claimed invention.

Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 1, 10 – 13, 41 – 47, 55 – 60, and 68 – 74 are rejected under **35 U.S.C. 112, first paragraph**, because the specification, while being enabling for a nucleic acid molecule that comprises a sequence encoding a CD80 mutant protein comprising "80V that is the variable domain of CD80," "86V that is the variable domain of CD86," etc., does not reasonably provide enablement for a molecule comprising "80V that is the variable domain of CD80 or a functional fragment thereof," "86V that is the variable domain of CD86 or a functional fragment thereof," etc.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized in *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, limited working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

The instant claim language encompasses "functional fragments" of various domains of CD80 and CD86.

However, the specification does not appear to have provided sufficient guidance as to which fragments of domains CD80 or CD86 would share the activity of the complete domains. Neither does the specification appear to have provided any working examples of any functional fragments. Thus it would require undue experimentation of the skilled artisan to determine which fragments would have the function of the respective domain. For example, Metzler et al. (Nature Structural Biol., 1997, 4: 527-531) show that numerous specific amino acids of CTLA4 are essential for its ability to

interact with its ligands CD80 and CD86 (see entire document, in particular, e.g. Table 2). Thus it is unpredictable if any functional activity will be shared by fragments which are smaller than the complete functional domains of a protein.

Further, the term "comprising" is open-ended and extends the molecule to include additional non-disclosed sequences on either or both sides of the disclosed region. As the term "comprising" is applied to sequences other than complete defined domains of CD80 or CD86, there does not appear to be sufficient guidance in the specification as filed as to how the skilled artisan would make and use the various fragments encompassed by the instant claims. A person of skill in the art would not know which sequences are essential, which sequences are non-essential, and what particular sequence lengths identify essential sequences. Without detailed direction as to which sequences are essential to the function of the domain, a person of skill in the art would not be able to determine without undue experimentation which of the plethora of polypeptide sequences encompassed by the instant claims would share the function of the respective complete protein domain.

14. Claims 10 – 13 and 41 are rejected under **35 U.S.C. 112, first paragraph**, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention.

It is noted that the recitation "**a** nucleic acid molecule of claim 1" in claims 10 and 13 is interpreted to encompass nucleic acids as specified in claim 1 or any portion (fragment) of a nucleic acid specified in claim 1. Therefore, claims 10 and 13, and claims dependent thereon, are subject to rejection under 35 USC 112, first paragraph, on the same grounds as set forth in section 13 above.

Specifically, the disclosure does not appear to have provided sufficient guidance as to which fragments of domains CD80 or CD86 would share the activity of the complete domains. Neither does the specification appear to have provided any working examples of any functional fragments. Thus it would require undue experimentation of the skilled artisan to determine which fragments would have the function of the respective domain. For example, Metzler et al. (Nature Structural Biol., 1997, 4: 527-531) show that numerous specific amino acids of CTLA4 are essential for its ability to interact with its ligands CD80 and CD86 (see entire document, in particular, e.g. Table 2). Thus it is unpredictable if any functional activity will be shared by fragments which are smaller than the complete functional domains of a protein.

Further, the term "comprising" is open-ended and extends the molecule to include additional non-disclosed sequences on either or both sides of the disclosed region. As the term "comprising" is applied to sequences other than complete defined domains of CD80 or CD86, there does not appear to be sufficient guidance in the specification as filed as to how the skilled artisan would make and use the various fragments encompassed by the instant claims. A person of skill in the art would not know which sequences are essential, which sequences are non-essential, and what particular sequence lengths identify essential sequences. Without detailed direction as to which sequences are essential to the function of the domain, a person of skill in the art would not be able to determine without undue experimentation which of the plethora of polypeptide sequences encompassed by the instant claims would share the function of the respective complete protein domain.

15. Claims 13, 47, 60, and 74 are rejected under **35 U.S.C. 112, first paragraph**, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention.

The specification does not provide a sufficient enabling description of the claimed invention.

The instant claims are drawn to a "vaccine or attenuated vaccine" comprising a nucleic acid molecule of the invention. A skilled artisan at the time the invention was made was aware that a "vaccine" is a composition which has a prophylactic or therapeutic effect, i.e. the claimed nucleic acids must possess the properties of a prophylactically or therapeutically effective adjuvant.

The instant specification discloses at pages 49 – 51 that by injecting mice with plasmids encoding CD80 molecules lacking the C domain, some aspects of an immune response to an antigen are enhanced. Given the scope of the claims, limited working examples, the unpredictability in the art and the amount of experimentation required; the amount of direction or guidance provided in the instant specification is not seen as sufficient to enable one of skill in the art to make and use the claimed invention, i.e. to produce a "vaccine" which has a prophylactic or therapeutic effect, because it is unpredictable whether the claimed nucleic acids are usable as a prophylactically or therapeutically effective adjuvant. Fore example, Singh et al. (Nature Biotechnology, 1999, 17: 1075 – 1081; see entire document) review that many experimental adjuvants that appear effective in vitro or even those that progress to clinical trials, have proven too toxic for clinical use (see entire document, in particular, e.g. the abstract, and page 1075, second column, first paragraph).

Therefore, in view of the quantity of experimentation necessary, the unpredictability of the art, the lack of sufficient guidance in the specification, the limited working examples, and the limited amount of direction provided given the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

17. Claims 1 – 2, 10 – 13, and 41 – 47 are rejected under **35 U.S.C. 102(b)** as being anticipated by Linsley et al. (US Patent No. 5,580,756; 12/03/1996; see entire document), as evidenced by the instant specification at page 5, last paragraph.

Linsley et al. teach nucleic acids encoding a B7 polypeptide, an art-recognized alternative name for CD80 (see entire document, in particular, e.g. Example 3 at columns 26 – 27). Specifically, Linsley et al. teach DNA molecules encoding the amino acid sequence containing amino acids from positions 1 – 215 of B7/CD80 (e.g. columns 6 – 7, bridging paragraph). The instant specification discloses that the C region of CD80/B7 is made up of amino acids 155 – 223 (page 5, last paragraph). Therefore, the DNA molecules taught by Linsley et al. encode B7/CD80 polypeptides which lack a part of the C region, specifically amino acids 216 – 223, while comprising the IgV-like domain (80V). Therefore, the teachings of Linsley et al. anticipate the instantly claimed limitation of "comprising at least one of 80V, 80tm, and 80ct and free of functional 80C." Since Linsley et al. teach molecules of the same structure as instantly claimed, their functional properties (such as having properties of a vaccine, or inability to transmit a

negative signal associated with wild-type CD80) are inherently the same as those of the molecules instantly claimed.

Linsley et al. further teach that the above DNA molecules can be joined to DNA sequences encoding the constant region of immunoglobulin (Ig), to form a construct (i.e. plasmid) that can express B7-Ig fusion protein (e.g. columns 6 – 7, bridging paragraph). Since immunoglobulin is immunogenic, these teachings anticipate the instant claim language directed to "a coding sequence encoding an immunogen."

Linsley et al. teach that in order to achieve expression of the above plasmid constructs, they need to be transfected into host cells (e.g. column 7 lines 18 – 27). Inherent in these teachings are compositions comprising said plasmids, as the skilled artisan at the time the invention was made was aware that transfection of a host cell with a plasmid encompasses incorporating the plasmid into an appropriate composition.

Therefore, the reference teachings anticipate the instant claimed invention.

18. Claims 1 – 2, 10 – 13, 41 – 47, 55 – 60, and 68 – 74 are rejected under 35 **U.S.C. 102(e)** as being anticipated by Sharpe et al. (US Patent 6,294,660; see entire documents).

Sharpe at al. teach and claim nucleic acids encoding B7-1 polypeptides, an art-recognized alternative name of CD80 (see entire document, in particular, e.g. the Claims). In particular, Sharpe t et al. teach and claim nucleic acids encoding a form of B7-1/CD80 in which an IgC-like domain has been deleted (e.g. column 11 lines 16 – 36, and claims 7 and 8). B7-1 protein consists of an IgV-like domain, an IgC-like domain, a transmembrane domain, and a cytoplasmic domain (see e.g. columns 3 – 4, bridging paragraph, of Sharpe et al.), or, using the abbreviations of the instant application, 80V, 80C, 80tm and 80ct domains. Therefore, the IgC-deleted form of B7-1/CD80, taught by

Sharpe et al., anticipates the instantly claimed mutant CD80 protein comprising 80V, 80tm and 80ct and lacking a functional 80C.

Sharpe et al. further teach that the nucleic acids encoding deletion-containing forms of B7-1/CD80 can be incorporated into plasmids, which may further comprise coding sequences for other proteins (i.e. immunogens) operably linked to regulatory elements (e.g. section "Recombinant Expression Vectors" at columns 17 – 19). Since Sharpe et al. teach molecules of the same structure as instantly claimed, their functional properties (such as having properties of a vaccine, or inability to transmit a negative signal associated with wild-type CD80) are inherently the same as those of the molecules instantly claimed.

Sharpe et al. teach that the functional V-like domain (80V) encompasses amino acids 34 – 138, and the functional transmembrane and cytoplasmic domains (80tm and 80ct) encompass amino acids 242 – 288 (e.g. column 14 second paragraph). These amino acid ranges comprise the corresponding ranges recited in the instant claim 68, and as such, given the "comprising" language of the instant claims, anticipate the instantly claimed subject matter.

Sharpe et al. also teach host cells transfected with the plasmids encoding deletion-containing forms of B7-1/CD80 (e.g. columns 19 – 20). Inherent in these teachings are compositions comprising said plasmids, as the skilled artisan at the time the invention was made was aware that transfection of a host cell with a plasmid encompasses incorporating the plasmid into an appropriate composition.

Therefore, the reference teachings anticipate the instant claimed invention.

19. Conclusion: no claim is allowed.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILIA OUSPENSKI whose telephone number is 571-272-2920. The examiner can normally be reached on Monday-Friday 9 - 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

ILIA OUSPENSKI
Patent Examiner
Art Unit 1644

April 4, 2006

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4/14/06